VivaScope® 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation

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Declared competing interests of authors: none

Published July 2016
DOI: 10.3310/hta20580

Scientific summary

VivaScope® 1500 and 3000 for skin lesions

Health Technology Assessment 2016; Vol. 20: No. 58
DOI: 10.3310/hta20580

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Background

Skin cancer is one of the most common cancers in the UK. It is commonly classified into melanoma skin cancer (or malignant melanoma), which develops from pigmented cells in the epidermis, and non-melanoma skin cancer, which develops from cells that produce keratin. Non-melanoma skin cancer can be further divided into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Malignant melanoma, SCC and BCC make up > 95% of all skin cancers.

The main risk factor for developing skin cancer is exposure to ultraviolet radiation in the form of sunlight or from the use of sunbeds. Other factors include age, sex, ethnicity, occupation, and personal and family history of skin cancer.

According to clinical experts, when patients with suspicious skin lesions present at secondary care, they are first examined with a dermoscope, and those with benign lesions are discharged. However, if the results of dermoscopy and/or the clinical features give rise to concern, the lesions are surgically excised. Therefore, the importance of identifying truly positive lesions while curtailing the number of unnecessary biopsies cannot be overemphasised.

The VivaScope® imaging system is a non-invasive reflectance confocal microscopy (RCM) technology that is designed to capture highly magnified images. It is used in conjunction with dermoscopy to provide more accurate diagnosis, leading to fewer biopsies of benign lesions and earlier detection of skin cancers. It may also be used as a guide to surgery to provide more accurate presurgical margins, preventing unnecessarily large scars for skin cancers in anatomical areas where tissue preservation is of importance (e.g. face, hands, feet and genitals), and reducing the risk of recurrence.

Objectives

The following questions are addressed in the clinical effectiveness section of the diagnostic assessment report:

- What is the clinical effectiveness and cost-effectiveness of the VivaScope® 1500 (Caliber Imaging and Diagnostics, Rochester, NY, USA; Lucid Inc., Rochester, NY, USA; or Lucid Inc., MAVIG GmbH, Munich, Germany) and VivaScope® 3000 (Caliber Imaging and Diagnostics, Rochester, NY, USA) in diagnosing suspicious skin lesions?
- What is the clinical effectiveness and cost-effectiveness of VivaScope 3000 in defining the margins of dermoscopically equivocal skin lesions?

Although this report is mainly aimed at the current versions of VivaScope (1500 and 3000), VivaScope® 1000 (Lucid Inc., Rochester, NY, USA, or Lucid Inc., MAVIG GmbH, Munich, Germany) and 2500 (Caliber Imaging and Diagnostics, Rochester, NY, USA), which are earlier models of VivaScope 1500 and 3000, respectively, were also considered, as they may provide additional information on the current versions.

The eligible reference standard for the assessment of diagnostic accuracy and margin delineation was histopathology of the biopsy of the excised skin lesion.

Methods

This assessment comprises a systematic review of clinical effectiveness and cost-effectiveness studies, and the development of three de novo economic models.

Clinical effectiveness systematic review

Evidence for the clinical effectiveness of the interventions was identified by searching electronic databases (MEDLINE, EMBASE, and The Cochrane Library) from inception to 14 October 2014 and updated on 11 February 2015. The search strategy combined terms capturing the interventions and comparators of interest, and the target condition.

Randomised controlled trials and observational studies evaluating VivaScope were eligible for inclusion. Two reviewers independently screened all titles and abstracts according to the inclusion criteria. Two reviewers extracted data from included studies using a standardised data extraction form, and the two extractions were validated. The quality of included studies was assessed using the quality assessment of diagnostic accuracy studies tool, according to the Cochrane handbook for diagnostic test accuracy reviews [Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews*. The Cochrane Collaboration; 2013. URL: www.srdta.cochrane.org/handbook-dta-reviews (accessed 13 January 2015)].

Review methods

Extracted data from included studies and quality assessment for each study were presented in structured tables and as a narrative summary. Evidence on the following outcome measures was considered: diagnostic accuracy; number of biopsies performed and repeat biopsies (lesion diagnosis only); morbidity associated with biopsy or excision surgery; recurrence rate (lesion margin delineation only); adverse events from biopsy including infections; and health-related quality of life (HRQoL).

Assessment of cost-effectiveness

Evidence for the cost-effectiveness of the VivaScope in the diagnostic assessment of suspected skin lesions was identified by searching electronic databases (MEDLINE and EMBASE), from inception to October 2014. The Health Technology Assessment database and NHS Economic Evaluation Database were also searched for economic evaluations addressing the review question. The search strategy combined terms capturing the interventions and comparators of interest, and the target condition.

In addition, a de novo economic model was constructed in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) to estimate the cost-effectiveness of VivaScope 1500 and 3000 in lesion diagnosis and margin delineation. According to the study populations that were identified as most relevant for the economic evaluation of VivaScope, three separate 'part' economic models were developed:

1. use of VivaScope in the diagnosis of equivocal lesions suspicious of melanoma
2. use of VivaScope in the diagnosis of suspected BCC lesions following a positive or equivocal finding on dermoscopy
3. use of VivaScope for the margin delineation of lentigo maligna (LM) prior to surgical therapy.

The analysis adopted the perspective of the NHS and Personal Social Services. Costs consisted of intervention costs of VivaScope (including purchase and maintenance costs, costs of parts and consumables, staff training and staff time required for the examination), costs associated with the comparators of the analysis (such as costs of biopsy, histological examination and monitoring), costs of management of skin lesions following diagnosis, as well as costs incurred following the presurgical mapping of malignant skin lesions. All costs were expressed in 2014 prices.

The outcome measure of the economic analysis was the quality-adjusted life-year (QALY). The impact of the intervention and its comparators on people's HRQoL was associated with the potential distress from excision and/or diagnostic biopsy of a lesion, the anxiety while waiting for the diagnostic results, the unnecessary treatment of people with false-positive (FP) lesions, the progression of the disease in people with false-negative (FN) lesions and the permanent disutility because of scarring following surgical intervention of skin lesions on head or neck. Costs and outcomes were discounted at an annual rate of 3.5%.

Utility data were taken from a systematic review of the literature. The company (MAVIG GmbH, Munich, Germany) provided the costs associated with the intervention (VivaScope 1500 and 3000 imaging system), including the purchase price of the equipment and parts and maintenance costs.

Each of the 'part' models consisted of a decision tree, followed by a Markov model, which followed patients and measured future consequences (costs and outcomes) over their lifetime. Deterministic and probabilistic analyses of all three-part models were undertaken. All input parameters were tested in one-way sensitivity analyses; additional one-way sensitivity analyses were undertaken to estimate the impact of alternative scenarios and model assumptions on the results. Finally, two-way sensitivity analyses were carried out to test the impact of concurrently varying sensitivity and specificity of VivaScope in the diagnostic assessment of eligible skin lesions suspicious of melanoma or BCC on the cost-effectiveness results.

Results

Clinical effectiveness systematic review

Sixteen studies (13 from electronic databases and three from contacting clinical experts) met the inclusion criteria. Thirteen of the studies investigated VivaScope in diagnosing suspected or equivocal lesions, and three studies investigated VivaScope in lesion margin delineation.

Of the 13 studies on lesion diagnosis, six used VivaScope 1500 and one used VivaScope 1500 or 3000. For earlier versions of VivaScope, three studies used VivaScope 1000, and two studies used both VivaScope 1000 and VivaScope 1500. Only one study used VivaScope 2500.

The majority of the 16 included studies had a low risk of bias and low applicability concerns in patient selection, conduct of the index test and reference standard. However, concerning flow and timing, the risk of bias in the majority of the studies was unclear because of poor reporting and/or insufficient data.

The included studies were heterogeneous in terms of study design (e.g. RCM alone or RCM after dermoscopy), patient population (e.g. different prior history of melanoma) or reporting of results (e.g. patient based or lesion based). Thus, it was considered unfeasible to combined their results in a meta-analysis.

Diagnostic accuracy

Diagnostic accuracy was the most commonly reported outcome, reported as sensitivity, specificity, positive predictive value or negative predictive value. Other diagnostic accuracy data, such as FP, FN and true negative (TN) rates, were rarely reported and had to be estimated/calculated using other reported diagnostic data where possible.

Two studies that investigated the use of VivaScope for lesion diagnosis were deemed to be the most representative of clinical practice in the UK setting. These were validated by clinical experts and, therefore, formed the basis of the health economic analysis for diagnosis of malignant melanoma.

One of the two studies assessed the impact of VivaScope 1500 on dermoscopically equivocal lesions. Of the 343 lesions subjected to VivaScope examination, only 264 were excised (the remaining 79 lesions were followed up for 1 year but no melanoma was diagnosed). Based on the 264 excised lesions, dermoscopy plus VivaScope 1500 was significantly more sensitive than dermoscopy alone in the diagnosis of melanoma (97.8% vs. 94.6%; $p = 0.043$) and significantly more specific than dermoscopy alone in the diagnosis of non-melanoma (92.4% vs. 26.74%; $p < 0.000001$). Alternatively, assuming that the 79 lesions followed up were TNs, the sensitivities (RCM 97.8% vs. dermoscopy 93.5%) were similar, while the specificity for VivaScope was higher (RCM 94.8% vs. dermoscopy 49.0%).

The second study prospectively assessed the potential impact of VivaScope 1500 in a routine melanoma workflow. At the dermoscopy, patients were referred to one of the following pathways:

- no further examination
- referral to RCM
    - RCM documentation (lesions with consistent suspicious clinical/dermoscopic criteria, already qualified and scheduled for surgical excision)
    - RCM consultation (equivocal, or moderately suspicious, lesions in which RCM diagnosis would determine the lesion-definite outcome, i.e. either excision or digital follow-up).

Of 491 lesions, 183 were referred for RCM documentation and 308 for RCM consultation. In the RCM documentation group, histopathology confirmed 110 RCM positives (23 melanomas, 19 BCCs and 68 benign lesions) and 73 RCM negatives (73 benign lesions).

In the RCM consultation group, RCM identified 81 positives (lesions diagnosed by RCM to be malignant) and 227 negatives (lesions diagnosed by RCM to be non-malignant). Of the 81 RCM positives, excision confirmed six melanomas, 19 BCCs and 56 benign lesions. Of the 227 RCM negatives followed up for 3–12 months, 28 showed significant changes but excision confirmed no malignancy, 178 showed no changes and 21 were lost to follow-up but checks at the local tumour registry identified no excision.

Based on the assumption that all the 21 RCM negatives lost to follow-up in the RCM consultation group were TNs, the sensitivity (RCM documentation 100% vs. RCM consultation 100%) and specificity (RCM documentation 51.77% vs. RCM consultation 78.6%) were calculated. However, when the 21 RCM negatives lost to follow-up were excluded, the sensitivity was 100% and specificity was 80.2% for RCM consultation.

One study that investigated the use of VivaScope 1500 in margin delineation was also deemed to be the most representative of clinical practice in the UK setting. Our clinical experts validated this and this trial formed the basis for the health economic analysis of VivaScope-assisted margin delineation.

This study analysed LM and LM melanoma (LMM) cases to determine whether or not VivaScope 1500 mapping might alter patient care and management. Out of 60 positive sites for LM confirmed by histopathology, 55 (FN = 5) had been confirmed by VivaScope 1500 and 21 (FN = 39) by dermoscopy, and, out of 125 LM sites confirmed as negative by histopathology, 121 (FP = 4) had been confirmed by VivaScope 1500 and 122 (FP = 3) by dermoscopy. Histopathology also showed that 17 out of 29 patients with visible lesions had evidence of subclinical > 5 mm beyond the edge of the dermoscopically identified margin. In addition, both the length and width of the dermoscopically visible area of the lesion were, on average, 60% smaller than that determined by VivaScope 1500.

Cost-effectiveness results

The systematic review on cost-effectiveness identified only one economic evaluation. The study estimated the impact of VivaScope use on the number of benign lesions needed to excise a malignant melanoma. The results indicated that VivaScope reduces the number needed to excise of skin lesions suspicious of melanoma and results in cost savings to the hospital. As the study was conducted in Italy, its findings may not be generalisable to the UK setting.

The results of primary economic modelling indicate that the cost-effectiveness of VivaScope in the diagnostic assessment of suspected melanomas was affected by the diagnostic accuracy data utilised in the model. Using the more 'optimistic' diagnostic data from Alarcon *et al.* (Alarcon I, Carrera C, Palou J, Alos L, Malvehy J, Puig S, *et al.* Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. *Br J Dermatol* 2014;**170**:802–8) resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £8877 per QALY (£9362 per QALY in probabilistic analysis), while the 'less favourable' diagnostic data from Pellacani *et al.* (Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. *Br J Dermatol* 2014;**171**:1044–51) resulted in a deterministic ICER of £19,095 per QALY (£25,453 per QALY in probabilistic analysis). VivaScope was also shown to be a dominant strategy when used for the diagnostic assessment of suspected BCCs with a positive or equivocal finding on dermoscopy.

Regarding margin delineation of LM, mapping with VivaScope was shown to be cost-effective, as indicated by a deterministic ICER of £10,241 per QALY (£11,651 per QALY in probabilistic analysis). When VivaScope was used for diagnosis as well as mapping of LM, then the intervention cost was reduced and it became a dominant strategy.

One-way sensitivity analysis showed that the most influential parameters across all models were those relating to permanent disutility as a result of scarring following surgical intervention of skin lesions on the head or neck (such as the percentage of people experiencing permanent disutility as well as the value of disutility itself) and the disutility because of anxiety while waiting for the results of biopsy.

Conclusion

VivaScope subsequent to dermoscopy may improve the diagnostic accuracy of equivocal skin lesions compared with dermoscopy alone, particularly for malignant melanomas. In terms of margin delineation, VivaScope 1500 mapping for LM and LMM may improve the accuracy in terms of complete excision of lesions compared with dermoscopically determined margins.

In addition, the use of VivaScope appears to be a cost-effective strategy in the diagnostic assessment of suspected skin cancer (more specifically, of suspected melanomas with an equivocal finding on dermoscopy and suspected BCCs with a positive or equivocal finding on dermoscopy) and the margin delineation of LM prior to surgical treatment, in particular when VivaScope is used for all three indications considered in the economic analysis.

Limitations

First, UK data are lacking in the included studies and, therefore, generalisability of the results to the UK population is unclear. This has implications for the NHS.

Second, apart from diagnostic accuracy and lesion recurrence rate (only reported by one study), none of the outcomes specified in the protocol was reported in the included studies.

Third, none of the included studies reported diagnostic accuracy results of SCC with VivaScope. This confirms evidence in the literature that suggest SCCs can be difficult to view using imaging techniques because their upper surface is often scaly, which can make it difficult to view detail at sufficient resolution.

Fourth, in some of the studies, there was a paucity of data and/or low quality of reported data on the number of patients with positive and negative test results, making it impossible to construct a 2×2 contingency table to calculate sensitivity and specificity.

Further research is also needed on the impact of diagnostic imaging systems on HRQoL in order to determine the cost-effectiveness of alternative diagnostic strategies in this area with higher certainty.

Study registration

This study is registered as PROSPERO CRD42014014433.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 14/69/02. The protocol was agreed in October 2014. The assessment report began editorial review in April 2015 and was accepted for publication in November 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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